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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Teresa Elisa Virginia Cabezon Silva

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GLAXOSMITHKLINE

CORPORATE INTELLECTUAL PROPERTY, MAI B482

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RESEARCH TRIANGLE PARK, NC 27709-3398

EXAMINER

BLUMEL, BENJAMIN P

ART UNIT

PAPER NUMBER

1648

NOTIFICATION DATE

DELIVERY MODE

05/26/2009

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/517,420	Applicant(s) CABEZON SILVA ET AL.	
	Examiner BENJAMIN P. BLUMEL	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 September 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 and 26-38 is/are pending in the application.
- 4a) Of the above claim(s) 7 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 8-19 and 26-38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 12/8/04 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>12/8/04 & 8/1/07</u> . | 6) <input checked="" type="checkbox"/> Other: <u>Notice to Comply</u> . |

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of the species election in the reply filed on February 29, 2008 is acknowledged. The traversal is on the ground(s) that the species possess Unity of Invention and they share a special technical feature and since no prior art has been cited and in view of the European patent as evidence that the invention has unity. This is not found persuasive because each choline binding domain and heterologous protein represents different species that require different searches and considerations with regard to the prior art. In addition, the heterologous proteins encompass unrelated proteins, (i.e., proteins from HIV, hepatitis C virus, tumor associated proteins, etc.).

The requirement is still deemed proper and is therefore made FINAL.

Claim 7 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/22/2008.

Claims 1-6 and 8-38 are examined on the merits. While applicants have labeled claims 2-4 and 26-35 as “(Withdrawn)”, the restriction requirement mailed on August 10, 2007 only required a species election be made and not an election of one group over another, therefore, the examiner has included the withdrawn claims during examination.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 12/8/04 & 8/1/07 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Objections

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The specification is objected to be the drawing description for figure 6 and pages 6, 47 and 61 lack does not contain a specific SEQ ID No:.

Applicants must comply with sequence rules in order to be considered a complete response to this Office Action.

Claim Objections

Claims 2, 3 and 4 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Since claim 1 requires SEQ ID NO: 8 (which contains SEQ ID NO: 2 between amino acids 6 and 26, the limitations of claims 2, 3 and 4 do not further limit since claim 2 includes derivatives of SEQ ID NO: 8 and claims 3 and 4 include other species that result in a broader scope than claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 37 recites, “A polypeptide according to claim 36 consisting of amino acid residues 5 to 133 of SEQ ID NO: 27.”, however, it is unclear how such a polypeptide can exist when claim 36 requires that a P2 or P30 epitope of a tetanus toxoid be associated with SEQ ID NO: 8. By stating that the polypeptide consists of amino acid residues 5 to 133 of SEQ ID NO: 27, such a recitation excludes P2 or P30 because this region of SEQ ID NO: 27 is SEQ ID NO: 8. The metes and bounds of the claim cannot be determined without further clarification/correction.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inducing immune responses to the claimed composition, does not reasonably provide enablement for treating cancer with the claimed composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

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The invention is drawn to a method of treating a patient suffering from cancer (such as prostate cancer or colorectal cancer, etc.) by administering a safe and effective amount of a nucleic acid expression vector that encodes a protein comprising SEQ ID NO: 8 and a tetanus toxin T helper epitope that is shorter than 141 amino acids in length. However, no working examples have been provided establishing that such an expression vector can treat someone suffering from cancer. In addition, the state of the art recognizes that for cancer/tumor treatments involving protein based therapies to be successful, a representative protein/antigen or a plurality of proteins/antigens need to be presented to the cancer patient's immune system. Such a requirement is taught by Ryan et al. (International Archives of Allergy and Immunology, 2007), in which they teach that selecting such a protein/antigen is critical for an effective and long lasting immune response. *See pages 182.* Therefore, without using immunogen that contains epitopes specific for a targeted cancer type, any reactive immune cells would not be directed towards the cancerous tissues. Furthermore, since the protein encoded by the vector of the present invention does not include any epitope or antigenic fragment associated with any tumor, additional research is required to determine how such an expression vector can treat any cancer in a patient.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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Claims 1, 5, 6, 8-19, 28-36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al. (US Pat. 6,395,278 B1) in view of Hoskins et al. (Journal of Bacteriology, 2001)-evidenced by Genbank accession # AAL00557, Vidarsson et al. (Infection and Immunity, 1998), Caubin et al. (Biotechnology and Bioengineering, 2001) and Panina-Bordignon et al. (European Journal of Immunology, 1989).

The claimed invention is drawn to a fusion protein comprising SEQ ID NO: 8 with a T helper epitope of a tetanus toxin (TT) inserted into SEQ ID NO: 8 as long as the protein is less than 141 amino acids long and a heterologous protein is chemically linked to the SEQ ID NO:8-TT protein. SEQ ID NO: 8 represents the C-terminus of the *Streptococcus pneumoniae* LytA protein. In addition, the fusion protein contains at least 4 histidine residues as an affinity tag. The claimed invention is also drawn to an expression vector that encodes the fusion protein and a host cell transformed with the expression vector. Furthermore, two different immunogenic/pharmaceutical compositions with adjuvants are claimed in which either the fusion protein or the expression vector are employed. The adjuvants used are 3D-MPL, QS21, or CpG. Lastly, the claimed invention involves methods of making and using such compositions for inducing immune responses. When inducing immune responses, the expression vector composition and the fusion protein composition can be administered one after another (i.e., prime-boost). During such an administration, the expression vectors can be administered by particle bombardment. For purposes of examination, the limitation of “tetanus toxin is inserted into said SEQ ID NO: 8” is interpreted as inserting within the protein or at one of the termini.

Xu et al. teach the creation of fusion proteins and expression vectors that contain the nucleic acid sequence for such fusion proteins in addition to the formulation of these products

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with adjuvants (such as 3D-MPL) and other pharmaceutical carriers in order to create immunogenic compositions. These fusion proteins can further contain multiple, different protein fragments and may also include T-helper cell epitope providing proteins. The basis for the fusion proteins revolves around tumor specific antigens, such as P502 and P501S (a truncated form of a prostate specific antigen). In order to complete the fusion protein, Xu et al. teach that a non-related protein should be coupled (either through recombinant DNA technology or through chemical conjugation). Xu et al. also suggest the use of affinity tags (such as poly histidine tags) for purifying fusion proteins. This non-related protein can be an immunological fusion partner, such as protein D of *H. influenzae* or the LytA protein from *S. pneumoniae*. Preferably, if the LytA protein is employed, the C-terminus (which contains the choline binding domains) would be used. This region is between amino acids 188 and 305. Xu et al. further teach that to induce immune responses towards the tumor antigen-fusion proteins, immunogenic compositions (i.e., DNA vectors or fusion proteins) can be administered multiple times over the course of several months. In addition, if DNA based compositions are employed, to improve their *in vivo* uptake, the DNA can be bound to biodegradable beads and/or gene guns can be employed to deliver the DNA compositions. However, Xu et al. do not teach the involvement of the tetanus toxin epitope P2 or P30 (a T-helper cell epitope) being inserted into SEQ ID NO: 8 and the resulting protein being shorter than 141 amino acid residues; or the heterologous administration of DNA and fusion proteins to a subject. *See columns 2, 3, 25-27, 31-33, 35 and 36.*

Hoskins et al. disclose the genome of *S. pneumoniae* R6, which expresses the autolysin (LytA) protein of SEQ ID NO: 8. Based on the sequence of this LytA external protein reported

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in Genbank accession AAL00557, SEQ ID NO: 8 resides in the C-terminus of residues 187 to 298.

Caubin et al. teach the development of chimeric *S. pneumoniae* LytA proteins by complexing the C-terminus (choline binding domains) with an affinity tag of 4 histidines. The region of the LytA protein stretched from amino acid 188 to 305 (a region of 117 amino acid residues). In order to produce these recombinant proteins, Caubin et al. employ yeast cells that contain the expression vectors necessary for protein production. *See pages 164 and 165.*

Vidarsson et al. teach the analysis of chemically conjugated *S. pneumoniae* polysaccharide Pn6B-TT as a vaccine. When compared to Pneumo23, Pn6B-TT induced higher IgG1 and IgM antibody titers in adults. In infants following a prime-boost protocol, IgG antibody titers were high enough to suggest a therapeutic potential of the chimeric immunogen. *See page 2869.*

Panina-Bordignon et al. teach the capability of tetanus toxin epitopes P2 (13 amino acids long) and P30 (20 amino acids long) to be universal immunogenic epitopes with regard to the ability of T cells to discriminate between whether or not each epitope is bound to MHC II molecules. *See abstract.*

It would have been obvious to one of ordinary skill in the art to modify the compositions and methods taught by Xu et al. in order to fuse TT P2 or P30 and P501S to SEQ ID NO: 8 and employ this fusion protein and its corresponding expression vector in a heterologous prime-boost immunization protocol. One would have been motivated to do so, given the suggestion by Xu et al. that the fusion proteins containing fusion partners with T-helper cell epitopes and/or the C-terminus of the LytA protein and tumor associated antigens, such as P501S, in order to form an

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immunogenic composition and the use of the fusion protein or its expression vector in the immunization over several administrations against tumor antigens. There would have been a reasonable expectation of success, given the knowledge that Hoskins et al. teaches the claimed C-terminus domain of SEQ ID NO: 8 between residues 187 and 298; also given the knowledge that chimeric LytA fragments of *S. pneumoniae* can be conjugated to a poly histidine tag, as taught by Caubin et al.; also given the knowledge that by chemically conjugating a tetanus toxin to *S. pneumoniae* saccharide Pn6B, the fusion complex generates an effective immune response in adults and infants following multiple administrations, as taught by Vidarsson et al.; and also given the knowledge that TT P2 and P30 are unique T cell recognizable epitopes, as taught by Panina-Bordignon et al. Furthermore, based on the teachings of Xu et al., Vidarsson et al. and Panina-Bordignon et al., the formation of a protein smaller than 141 amino acids but containing SEQ ID NO: 8 and P2 or P30 would be expected since any fusion protein made up from these fragments would not exceed 140 residues in length. In addition, while Xu et al. and Vidarsson et al. teach prime-boost immunization protocols, one skilled in the art would apply differential immunizations between expression vectors and their encoded proteins in order to optimize the sensitivity of any elicited immune response. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BENJAMIN P. BLUMEL whose telephone number is (571)272-4960. The examiner can normally be reached on M-F, 8-4:30.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stacy B Chen/
Primary Examiner, Art Unit 1648

/BENJAMIN P BLUMEL/
Examiner
Art Unit 1648